REMARKS

I. Overview

Applicants have reviewed and considered the Office Action dated December 12, 2008. Additional claims 102 and 103 have been added. Support for these additional claims can be found throughout the published application, patent application publication no. 20040191229, for example in paragraphs 10, 57, 115, 205, and Table 2. Upon entry of this amendment, claims 1-74, 85 and 99-103 are pending in the instant application. Applicants respectfully request reconsideration of the above-identified application in view of the remarks that follow.

II. Claim Rejections Under 35 U.S.C. § 103

A. Claims 1-4, 34, 67, 85, and 99 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over LaTemple-II (LaTemple-II, D.C. et al., Cancer Research, 56:3069-3074, 1996; cited in the IDS) in view of Link, Jr.-II (Link, Jr., et al., US 5,869,035A; issued 2/9/1999; of record), in view of Larsen (Larsen, R.D. et al., Proc. Natl. Acad. Sci., USA, 86:8277-8231, 1989), and further in view of ATCC (ATCC Cell Lines and Hybridomas, 8th edition, 1994, page 100; of record).

The Examiner states LaTemple-II teaches a method of using melanoma cells lines undergoing stable transfection with α-1,3GT *c*DNA as vaccinating cell lines, where the stably transfected cell lines are an alternative to autologous tumor cells or cell membranes treated with neuraminidase, recombinant α-1,3GT and UDP-Gal (see page 3073, lst col., last paragraph) and lethal irradiation. The Examiner states thus, LaTemple-II provides the concept of irradiated tumor cell lines to transfected with an α-1,3GT encoding polynucleotide sequence, and its use as a tumor therapeutic composition. The Examiner states that Link, Jr.-II teaches a retroviral vector the same as SEQ ID NO: 1, and Larson teaches the cDNA encoding murine α-1,3GT enzyme, and ATCC teaches A549 cells.

The Examiner states it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used A549 cells in the methods of Link, Jr.-II to make a pharmaceutical composition for inhibiting tumor growth, where the A549 cells have been transformed with an α-(1,3) galactosyltransferase encoding sequence to make cells that α-gal epitopes as taught by LaTemple-II, because LaTemple-II suggest transforming tumor cells and because Link, Jr.-II demonstrates the method with a tumor cell line, the A549 cell line.

Applicants respectfully submit that the rejection is improper and the claimed invention is not obvious because the use of allogeneic vaccines was discouraged in the art, the results achieved in the present application are unexpected in light of the teachings in the art, and combining Link, Jr.-II with LaTemple-II would change the principle of operation of Link, Jr.-II .

1. The Art Actively Taught Away From the Use of Allogeneic Anti-Cancer Vaccines

The claimed invention is not obvious as the art actively taught away from the use of allogeneic anti-cancer vaccines. When making a determination of obviousness the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. *In re Young*, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991). Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966).

Applicants' claims are drawn to a pharmaceutical composition derived from "human tumor cell lines." Because cell lines are being used, the pharmaceutical composition will necessarily be derived from a subject other than the intended recipient. As a result, the vaccines claimed in the present invention are allogeneic, not autologous vaccines.

The Examiner cites one sentence at the end of LaTemple-II which states that "[a] similar *in vivo* opsonization may be achieved with vaccinating cell lines (e.g., melanoma cell lines) treated with neuraminidase and rα1,3GT or undergoing stable transfection with α1,3GT cDNA, as we have described previously (53)." (LaTemple-II, at page 3073, Office Action dated December 12, 2008, at page 5). The Examiner uses this sentence to establish that that there was some motivation or desire to create allogeneic cancer vaccines in the field. The Applicants note that the passing comment by LaTemple-II expresses considerable uncertainty as to the potential success of this approach and at best invites further research in the area.

Further research performed in the art clearly demonstrated that allogeneic vaccines were dangerous and ineffective when used as an anti-cancer vaccine. Galili, a reference published after LaTemple-II but before the present application, teaches that there were concerns that allogeneic cells would result in the introduction of pathogens into patients that were treated with the allogeneic vaccines. Galili, U. et al., Journal of Hematotherapy & Stem Cell Research 10:501-511 at 508 2nd Col., 2001, submitted by the Applicants in an IDS on June 10, 2004. Furthermore, Galili teaches that it is desirable that the cells used in the vaccine be as similar to the tumor cells from the patient as possible so as to limit side effects and increase efficacy. Galili, page 508, 2nd Col. The cells in the claimed therapeutic compositions are from entirely different tumors in entirely different subjects and, as such, differ significantly from the tumor cells from the patient.

The Applicants submit that Galili effectively discredits any motivation to use allogeneic vaccines set forth in LaTemple-II. The extensive discussion of the dangers and undesirability of using allogeneic vaccines overcomes LaTemple-II's passing mention of an alternative embodiment. Specifically, Galili gives explicit reasoning and analysis in support of the position that allogeneic vaccines are dangerous and undesirable. Additionally, under 35 U.S.C. § 103 the Examiner is to determine "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious **at the time the invention was made** to a person having ordinary skill in the art to which said subject matter pertains." (emphasis added). Because Galili is closer in time to the present application Galili more accurately represents the knowledge in the art at the time of invention.

The Applicants respectfully submit that, in light of Galili, one skilled in the art at the time of the invention upon reading the passing comment in LaTemple-II would not have been motivated to develop whole cell allogeneic cancer vaccines. In fact, Galili would have expressly guided one of ordinary skill away from the present invention using allogeneic cells and towards using autologous cells.

In view of the above, Applicants submit that considering LaTemple-II in view of the totality of the prior art, LaTemple-II fails to make the invention obvious as one skilled in the art using allogeneic cells would have been proceeding contrary to the accepted wisdom in the art.

2. The Results Obtained by the Applicants Are Unexpected in Light of the Teachings in the Art

The claimed invention is not obvious as the results obtained by the Applicants are unexpected in light of the teachings in the art. "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). The Applicants respectfully submit that the claimed invention is not obvious as the prior art taught that allogeneic vaccines would not be effective.

Chamberlain, another reference published after LaTemple-II and before the filing date of the present application, states that as of 2000 seven trials involving cancer vaccines were significant enough to "deserve mention." Chamberlain, R.S. et al., Expert Opinion on Pharmacotherapy, 1(4): 603-614, 2000 at page 606, 1st Col. See Chamberlain cited by the Examiner in the instant case in the Office Action dated January 3, 2007. The summarized trials covered three autologous anticancer vaccines and four allogeneic vaccines. Chamberlain, at page 606. The three autologous anticancer vaccines showed positive clinical results and were advancing through the clinical trial process. Chamberlain, at page 606. The four allogeneic vaccines performed significantly worse, producing results characterized as "no difference ... between groups", "disappointing", and "not clinically significant." Chamberlain, at page 606. Thus, due to these discouraging outcomes there was no reasonable expectation of success that an allogeneic vaccine would even have any level of success, much less be successful in preventing or treating tumors. Thus, LaTemple-II and art such as Chamberlain known at the time of filing do not provide one of ordinary skill in the art a reasonable expectation of success for the claimed compositions. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP §§ 2142 and 2143.02.

In contrast, the claimed therapeutic compositions have unexpectedly positive results from the use of vaccines based on cancer cell lines. Applicants respectfully direct the Examiner's attention to Examples 6 and 7 in the specification which show the prevention of subcutaneous tumors by vaccination with α Gal $^{(+)}$therapeutic compositions and the successful treatment of pre-established subcutaneous melanoma tumors by vaccination with α Gal $^{+}$ therapeutic compositions. Further, Applicants demonstrate that the compositions of the invention are useful in treating metastasized tumors. See Example 5 in the specification as originally filed. These results show that, contrary to the teachings and expectations in the art, alphaGal allogeneic vaccine compositions comprising cancer cell lines are effective in the prevention and treatment of cancer. Thus, claims 1, 3, 4, 66, 85 and 99 are not obvious.

3. Combining Link, Jr.-II With LaTemple-II Would Change the Principle of Operation of Link, Jr.-II

The claimed invention is not obvious because combining Link, Jr.-II with LaTemple-II would change the principle of operation of Link, Jr.-II . If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). The Applicants submit that Link, Jr.-II represents a "suicide gene therapy" approach to cancer treatment whereas LaTemple-II discusses a true cancer vaccination strategy.

The entire focus of Link, Jr.-II is the transformation of the tumor cells, preferably *in vivo*, in order to cause the complement-mediated destruction of the transformed cells. Link, Jr.-II , at page 1, lines 6-11. While this does involve the use of the immune system, this approach is more targeted than LaTemple-II where the hope was that the "anti-Gal mediated uptake of any vaccinating membrane by APCs with Fc receptors may ultimately enable the effective processing and presentation of the TAA in the tumor vaccine." LaTemple-II, at page 3073, paragraph 3, last sentence. The goal of a vaccination strategy like LaTemple-II is to have the patient's immune system learn to recognize the patient's own tumor cells through opsonization of the α-gal positive autologous cells. The theory being that once the patient's immune system learns the TSAs, the immune system will continue to attack the patient's tumor even though the remaining tumor cells do not express α-gal.

In a complement mediated approach such as Link, Jr.-II , the goal is to have the patient's immune system directly recognize and destroy the patient's α-gal positive cells. Because Link, Jr.-II teaches the complement mediated approach, it would simply not make sense to first irradiate the α-gal positive cells and then inject them into the patient as the irradiation would have already killed the cells. Additionally, this approach would change the principle of operation for Link, Jr.-II from a suicide gene therapy approach to a cancer vaccination approach.

As set forth above, the art actively taught away from the use of allogeneic vaccines and regarded them to be dangerous. Additionally, the art taught that allogeneic vaccines were not effective. Finally combining Link, Jr.-II with LaTemple-II would change Link, Jr.-II 's principle of operation from suicide gene therapy to cancer vaccination. ATCC and Larsen, also cited by the Examiner, also fail to supply the missing motivation to combine the references and expectation of success. As a result, the claimed invention is not obvious. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-4, 34, 67, 85 and 99 under 35 U.S.C. 103(a).

B. Claims 1-4, 34, 67, 85, and 99 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over LaTemple-II (LaTemple-II, D.C. et al., Cancer Research, 56:3069-3074, 1996; cited in the IDS) in view of Link, Jr.-II (Link, Jr., et al., US 5,869,035A; issued 2/9/1999; of record), in view of Larsen (Larsen, R.D. et al., Proc. Natl. Acad. Sci., USA, 86:8277-8231, 1989), in view of ATCC (ATCC Cell Lines and Hybridomas, 8th edition, 1994, page 100; of record), and further in view of Berd (US 6,333,028; issued 12/25/2001; effective filing 8/14/1998; of record).

The Examiner states the combination of LaTemple-II, and Link, Jr.-II and ATCC teach the composition of claims as set forth above and Berd teaches the use of adjuvants in hapten modified tumor cells, where the adjuvants are BCG, QS-21 or IL-12, for example (see col. 8, lines 40-51). The Examiner states, therefore it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the compositions that are taught by the combination of LaTemple-II, Link, Jr.-II, Larsen and ATCC, because the use of adjuvants for tumor cell-based vaccines is known in the art, and because adjuvants are known in the art to increase an immune response to components of vaccine compositions.

As discussed previously, the totality of the prior art teaches away from using allogeneic cells in vaccines. Berd et al. fail to supply the teachings that are lacking in LaTemple-II, Link, Jr.-II, Larsen and ATCC. Thus, the claimed invention is not obvious.

Further, as discussed previously, the prior art references, alone or combined, fail to provide a reasonable expectation of success for a therapeutic composition of modified allogeneic cells for inhibiting tumor growth and stimulating an immune response. M.P.E.P. § 2143.02.

Accordingly, the claimed invention is not obvious and the rejection of claims 1-4, 34, 67, 85, and 99 should be reconsidered and withdrawn.

C. Claims 1-4, 34, 67, 85, and 99-101 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over LaTemple-II (LaTemple-II, D.C. et al., Cancer Research, 56:3069-3074, 1996; cited in the IDS) in view of Link, Jr.-II (Link, Jr., et al., US 5,869,035A; issued 2/9/1999; of record), in view of Larsen (Larsen, R.D. et al., Proc. Natl. Acad. Sci., USA, 86:8277-8231, 1989), in view of ATCC (ATCC Cell Lines and Hybridomas, 8th edition, 1994, page 100; of record), and further in view of Pardoll (US 6,187,306; effective filing date of 8/16/1996).

The Examiner states the combination LaTemple-II, and Link, Jr.-II and ATCC teach the composition of claims as set forth above. The Examiner states, however, the use of more than one cell line in a tumor vaccine is known in the art as evidenced by the teachings of Pardoll (see col. 11, lines 40-49), which teaches that a cell vaccine comprising a multiplicity of cell lines is a preferred composition. The Examiner states, therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used a combination of at lest two cells lines to make a composition for use in the treatment of cancer via the induction of an immune response.

In this rejection, the Examiner cites in addition to the LaTemple-II, and Link, Jr.-II and ATCC references, Pardoll and essentially makes the same arguments for the use of tumor cell lines in a vaccine. Office Action, July 15, 2008, at page 9.

As discussed previously, the totality of the prior art teaches away from using modified allogeneic cells in vaccines. As discussed above, the prior art references, alone or combined, fail to provide a reasonable expectation of success for a therapeutic composition of modified allogeneic cells for inhibiting tumor growth and stimulating an immune response. M.P.E.P. § 2143.02. Pardoll fails to supply the teachings that are lacking in LaTemple-II, Link, Jr.-II, Larsen and ATCC. Accordingly, the claimed invention is not obvious and the rejection of claims 1-4, 34, 67, 85, and 99-101 should be reconsidered and withdrawn.

III. Additional claims

Claims 102-103 have been added and are believed to be patentable over the references made of record at least for the reasons set forth above, plus the elements in the claims. Claim 102 recites: "cells are present in the composition in an amount effective to treat a pre-existing tumor". Support for these additional claims can be found throughout the published application, patent application publication no. 20040191229, for example in paragraphs 10, 57, 115, 205, and Table 2.

IV. Double Patenting

Claims 1-5, 66-68, 85, and 99-101 remain provisionally rejected on the ground of Nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-14 of co-pending Application No. 11/013,685.

Applicants will be pleased to address this rejection upon a Notice of Allowance.

V. Conclusion

This is a request to extend the period for filing a response in the above-identified application for one month from March 12, 2009 to April 12, 2009. Applicant is a small entity;

therefore, please charge Deposit Account number 26-0084 in the amount of $65.00 to cover the cost of the one month extension.

No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

JANAÉ E. LEHMAN BELL, Ph.D., Reg. No. 55,370
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No: (515) 288-3667
Fax No: (515) 288-1338

CUSTOMER NO: 22885
Attorneys of Record

- bjh -
Enclosures